REMARKS

Entry of the claim amendments is respectfully requested. No new matter is added.

Claims 2-21 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for requiring the administration of a viable strain without indication of the mode of administration. Claims 2 and 4 have been cancelled, and claims 3 and 17 have been amended to indicate that the DSM 6601 is administered orally, as suggested by the Examiner. No new matter has been added. Reconsideration and withdrawal of this ground of rejection are therefore respectfully requested.

Claims 2-10 and 17-18 are rejected under 35 U.S.C. § 102(b) as anticipated by *Hockertz* or *Lodinova-Zadnikova et al.* or under 35 U.S.C. § 102(a) as being anticipated by DE 196 37 936. With respect to *Hockertz*, the Examiner appears to primarily base the rejection on the doctrine of inherency, as it is plain that the reference does not discuss either gastro-intestinal infections or note any gastro-intestinal complications such as diarrhea, but is merely directed to the treatment of a systemic *Candida* infection. The reference pertains to the immune modulatory effect of orally administered *E. coli* strain DSM 6601 against intravenously induced *Listeria* monocytogenes or *Candida* infection. It is reported that pathogen counts found in the respective organs, namely the liver and spleen, may be ameliorated by a single previous *E. coli* challenge. In this mouse model system, *intravenously* administered *Listeria* and/or *Candida* induce a *systemic* inflammation. Infection of the gastro-intestinal track by *Listeria* and/or *Candida* and associated diarrhea do not develop nor are reported in this model.

Despite the deficiencies, the Examiner, using

hindsight, concludes that the oral administration of viable *E. coli* DSM 6601 in a therapeutically effective amount inherently prevents and/or treats diarrhea in a mammal. As such, the Examiner's is attempting to overcome the deficiencies of *Hockertz* by contending that the administration of DSM 6601 to mice would necessarily and always prevent diarrhea and therefore anticipate the claimed methods. To accept this, one would also have to argue that the administration of DSM 6601 would inherently teach a method of treatment for all diseases. This is absolutely contrary to the case law.

Anticipation requires that each and every element set forth in a claim must be found, either expressly or inherently, in a single prior art reference. *In re Robertson*, 169 F.3d 743, 745, 49 U.S.P.Q.2d 1949 (Fed. Cir. 1999). Although a reference may still anticipate if the element is inherent in its disclosure, to establish inherency, the extrinsic evidence "must make clear that the missing descriptive matter is necessarily present in the thing described in the reference and that it would be so recognized by persons of ordinary skill in the art." *Continental Can Co. v. Monstanto Co.*, 948 F.2d 1264, 1268, 20 U.S.P.Q.2d 1746, 1749 (Fed. Cir. 1991). Inherency "may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." *Continental Can Co.*, 948 F.2d at 1269, 20 U.S.P.Q.2de at 1749 (quoting *In re Oelrich*, 666 F.2d 578, 581, 212 U.S.P.Q. 323, 326 (C.C.PA. 1981)). The Examiner has provided no evidence to support the legal conclusion of inherency. Therefore, it is entirely improper to merely allege something is inherent and force Applicant to try to prove the negative.

With respect to the issue of whether patents to second medical uses are patentable, Applicant acknowledges that each

patent is examined on its own merits. However, while *Hockertz* teaches that in a mouse model system oral administration of DSM 6601 may be effective in treating a *systemic Candida* infection, it was in no way contemplated that DSM 6601 would prove to have a prophylactic or therapeutic effect upon diarrhea caused by a fungi. At a minimum, both the "patient and/or biochemical pathway/mechanisms of actions" are plainly not substantially the same between *Hockertz* and the claimed invention. As such, the contention that the method of *Hockertz* would inherently prevent diarrhea in a mammal which suffers from *intestinal* colonization by pathogenic fungi is unfounded. *Hockertz* cannot anticipate the claimed invention.

With respect to *Lodinova-Zadnikova et al.*, Applicant again notes that this reference merely teaches administration of DSM 6601 to newborn babies to prevent or reduce colonization of the gastro-intestinal tract by pathogenic *bacteria*. The reference reports that prophylactic administration of the DSM 6601 reduced pathogenic bacteria load.

Clearly, the reference fails to discuss the use of *E. coli* to prevent or treat diarrhea caused by fungi in the intestinal tract. Moreover, none of the newborns studied were suffering from intestinal colonization of pathogenic bacteria, or more importantly fungi, as required by all of the claims. In view of this alone, *Lodinova-Zadnikova et al.* cannot anticipate the claimed invention.

Moreover, with respect to the Examiner's contention that *Lodinova-Zadnikova et al.* suggests that at least competitive exclusion is taught by *Lodinova-Zadnikova et al.*, this would apply only to pathogenic bacteria, and in no way relates to the intestinal colonization of a pathogenic fungi. Therefore, it is plain that this reference neither teaches nor suggests that DSM 6601 may be used for the treatment or

prevention of diarrhea or the intestinal colonization of pathogenic fungi. Moreover, there is nothing to suggest that the treatment disclosed in the reference would necessarily and always result in antimycotic activity for the prevention of diarrhea. As such, *Lodinova-Zadnikova et al.* cannot anticipate the claimed invention.

Finally, with respect to DE 196 37 936, Applicant again notes that this reference discloses a pharmaceutical preparation with at least one active substance (nystatin) and one natural bioadhesive component (DSM 6601) for the application to mucosal surfaces. Specifically, it is disclosed that the *combination* of nystatin and DSM 6601 reduced fungal load of the intestine by a single administration. The reference does not, however, disclose the use of DSM 6601 as a fungicidal means, but rather appears to teach away therefrom, since an antimycoticum, namely nystatin, is *required* for this effect.

At most, the reference teaches that DSM 6601 is useful to "support" the antimycotic treatment of intestinal *Candida* infection with nystatin. (*See* p. 12.) It is plain, therefore, that DSM 6601 is clearly to be used only as an auxiliary substance, not as the medicinally effective component. The active component is nystatin. Therefore, the reference does not teach the administration of DSM 6601 alone to treat an intestinal fungal infection, as the reference makes clear that the nystatin is necessary for the antimycotic properties of the pharmaceutical preparation. In this regard, Applicant notes that the reference directs the "bioadhesive component" (DSM 6601) to be *coupled to* the "*effective substance*" (nystatin), chemically or otherwise, to form the pharmaceutical preparation. The DSM 6601 is not administered alone or in its natural form. As such, the method taught in the reference does not necessarily provide anti-fungal activity, and it clearly

does not teach administering a therapeutically effective amount of uncoupled, natural *E. coli* DSM 6601 to treat or prevent diarrhea mediated by pathogenic fungi in a mammal that suffers from intestinal colonization of the pathogenic fungi as required by all the pending claims. As such, this reference cannot anticipate the claimed invention. Reconsideration and withdrawal of the rejection are therefore respectfully requested.

Finally, claims 2-21 are rejected under 35 U.S.C. § 103(a) as being obvious over *Hockertz* taken with *Lodinova-Zadnikova et al.* and DE 196 37 936.

The Examiner contends that *Hockertz* discloses the administration of DSM 6601 to mice, the administration of which has prophylactic effects on fungi such as *Candida* due to immunostimulation. The Examiner also contends that *Lodinova-Zanikova et al.* disclose the administration of DSM 6601 to humans, and that this administration has the effect of protecting mammals such as humans from diarrhea, which could include fungi-mediated diarrhea. Finally, the Examiner contends that DE 196 37 936 teaches the administration of DSM 6601 to treat intestinal infections with *Candida* infection, which is the same microorganism treated in the instant disclosure. The Examiner concludes that it would have been obvious to one of ordinary skill in the art to modify the process of preventing and/or treating diarrhea, including fungal diarrhea, of *Hockertz*, *Lodinova-Zadnikova et al.*, and DE 196 37 936 by providing viable *E. coli* DSM 6601 in therapeutically effective amounts to a ruminant such as bovines, for the expected economic benefit of maximizing the yield of agronomically valuable animals that are healthy and suitable for the production of milk for human consumption.

Applicant respectfully traverses this rejection. As

noted above, the problem underlying the present invention is to provide a means to combat effectively diarrhea caused by pathogenic fungi. The problem underlying the present invention is solved by a method for treating and preventing diarrhea caused by pathogenic fungi in mammals by orally administering to the mammal a therapeutically effective amount of *E. coli* strain DSM 6601. The novel method to treat diarrhea caused by pathogenic fungi may be used to treat or prevent diarrhea in mammals by the administration of viable *E. coli* strain DSM 6601. As the specification makes clear, after all existing therapeutic options had been exhausted, the occurrence of diarrhea due to gastroenteritides in suckling calves was prevented almost completely by the prophylactic and therapeutic application of a suspension of *E. coli* Strain DSM 6601 (see for example, pg. 10, lns. 5-8 of the instant specification). Significantly, none of the prior art documents teach the use of *E. coli* strain DSM 6601 to treat diarrhea caused by pathogenic fungi. DE 196 37 936 teaches one to use the *E. coli* strain DSM 6601 in *combination* with a pharmacologically active compound, particularly the mycostatic active antimycotic nystatin. Thus, by teaching the necessity of *both* the active compound and *E. coli*, but using the *E. coli* as a vehicle for the antimycotic compound, DE 196 37 936 teaches away from the present invention. Even if one accepted that DSM 6601 may have participated in the anti-*Candida* effect, one skilled in the art would not have doubted to attribute the anti-*Candida* effect to the antimycotic agent nystatin. There plainly is no teaching or suggestion in the reference to use the DSM 6601 alone in a therapeutically effective amount and therefore there is no teaching or suggestion to combine it with the other cited references.

In addition, even if one could combine the German reference with either *Hockertz* or *Ladinova-Zadnikova et al.*, the

combination does not render the claimed invention obvious. According to *Hockertz* and *Ladinova-Zadnikova et al.*, neither reference teaches gastro-intestinal infection by fungi causing diarrhea. Thus, neither reference teaches or suggests one skilled in the art to use *E. coli* strain DSM 6601 as a remedy for fungi-caused diarrhea. The Examiner has presented no evidence or support for the contention that one of ordinary skill in the art would reasonably expect that at the time of the claimed invention, the administration of viable *E. coli* DSM 6601 would be effective throughout the body regardless of the intended target at the moment of administration. Moreover, there is plainly no teaching or suggestion in any of the references of a method for treating or preventing diarrhea mediated by pathogenic fungi which suffers from intestinal colonization of the pathogenic fungi by orally administering to the mammal a therapeutically effective amount of viable *E. coli* strain DSM 6601, nor to administer such strain for at least about 10 days. Reconsideration and withdrawal of this ground of rejection are therefore respectfully requested.

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue.

If, however, for any reason the Examiner does not believe that such action can be taken at this time, it is respectfully requested that she telephone Applicant's attorney at (908) 654-5000 in order to overcome any additional objections which he might have.

If there are any additional charges in connection with this requested amendment, the Examiner is authorized to charge Deposit Account No. 12-1095 therefor.

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Respectfully submitted,

By _____
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